

Breast Cancer Awareness

Most Women with Early-Stage Breast Cancer Avoid Extensive Lymph Node Removal

A study completed last year of women with early-stage breast cancer found that surgeons no longer universally remove most of the lymph nodes in the underarm area when a biopsy of the nearby lymph nodes shows cancer—a major change in breast cancer management. The study, which evaluated data from 2.7 million U.S. breast cancer patients, was published as in the *Journal of the American College of Surgeons*.

Until then, it was unclear to what extent surgeons were following the recommendations of a landmark clinical trial published more than four years ago, known as the American College of Surgeons Oncology Group Z0011, or ACOSOG Z-11, trial. Those researchers reported that most early-stage breast cancer patients with tumor in their sentinel lymph node (the first draining node) who undergo lumpectomy do not benefit from surgical removal of the remaining lymph nodes in the underarm area, called completion axillary lymph node dissection (ALND). That study found no difference in cancer recurrence and five-year survival between patients who underwent ALND and those who did not but were monitored for recurrences.

The study found a dramatic increase in the proportion of lumpectomy patients who underwent only a sentinel lymph node biopsy (SNB)—removal of the “gatekeeper” lymph nodes that the cancer is most likely to spread to first—without an ALND after discovery of cancerous sentinel nodes. According to the study authors, the SNB-alone rate more than doubled, from 23 percent in 2009, before publication of the first results of the ACOSOG Z-11 trial in September 2010, to 56 percent in 2011, the first year after publication.

“As far as I know, our study is the first to show that the findings from the ACOSOG Z-11 trial have changed clinical practice for breast cancer patients nationwide,” said lead author Katharine Yao, MD, FACS, director of the Breast Surgical Program at NorthShore University HealthSystem, Evanston, Ill., and clinical associate professor of surgery at the University of Chicago Pritzker School of Medicine. “The Z-11 trial has had a huge impact because of the lower risks for patients who undergo SNB alone.”

Removal of small numbers of lymph nodes in SNB alone, according to Dr. Yao, greatly lowers the lifetime risk of developing the often disabling complication of lymphedema. This buildup of lymph fluid under the skin results

in swelling and sometimes pain.

For the study, Dr. Yao and colleagues used the National Cancer Data Base (NCDB), a joint project of the American College of Surgeons Commission on Cancer (CoC) and the American Cancer Society. NCDB captures an estimated 70 percent of newly diagnosed cancer cases in the United States from approximately 1,500 cancer programs accredited by the CoC.

Although NCDB does not identify the type of lymph node dissection (SNB or SNB plus ALND) performed, the researchers used the number of lymph nodes removed as surrogates for these procedures. They categorized the removal of four or fewer lymph nodes as SNB only and removal of 10 or more nodes as ALND.

From the 2.72 million breast cancer cases diagnosed between 1998 and 2011 and listed in the database, the investigators found that 74,309 patients met the Z-11 trial’s eligibility criteria for having SNB alone. These patients underwent lumpectomy and radiation therapy to the whole breast; had tumors 5 centimeters or smaller (less than 2 inches) that appeared clinically node negative; had negative surgical margins (no cancer cells seen at the outer edge of the breast tissue removed); and had two or fewer tumor-positive sentinel lymph nodes.

The rate of SNB alone reportedly increased from 6.1 percent in 1998 to 56 percent in 2011, the most recent data at the time of the study. Because the Z-11 trial results were new in 2011, Dr. Yao said she expects the rate will have increased further in 2012.

Statistical analyses revealed that lumpectomy patients were more likely to undergo ALND if they had any of the following characteristics considered high risk: age younger than 50; black race; triple negative tumors (absence of the three most common types of receptors known to fuel most breast cancer growth); and larger tumors (3 cm or less). In addition, patients with two positive sentinel lymph nodes were twice as likely to have an ALND as patients with one tumor-positive sentinel node. Patients whose tumor metastases measured 2 mm (the width of two grains of rice) or larger were more than three times likelier to undergo ALND compared with patients who had a smaller spread of the cancer, called micrometastases.

Dr. Yao said their findings suggest that some practitioners may feel uncomfortable not performing ALND in



high-risk patients, although the Z-11 trial included them. She called for more education for surgeons regarding the applicability of the Z-11 trial findings to these high-risk subgroups and for longer follow-up of these high-risk patients.

The researchers also analyzed 400,052 breast cancer cases that did not meet one of the Z-11 trial’s eligibility criteria. Dr. Yao said these results were “somewhat surprising.”

They reported that more than 22 percent of patients who underwent a mastectomy in 2011 had only SNB despite mastectomy patients not being included in the Z-11 trial. In addition, SNB without ALND occurred in more than 50 percent of patients who had tumors larger than the recommended 5 cm or those who received no or partial radiation therapy, rather than whole-breast irradiation.

“It is a little concerning that patients who fall outside the Z-11 eligibility criteria are getting SNB alone,” Dr. Yao said. “It’s controversial to perform SNB alone in mastectomy patients because we don’t know if it affects overall outcomes.”

Information for this article was provided by the American College of Surgeons.

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NCI Launches Largest-Ever Study of Breast Cancer Genetics in Black Women

The largest study ever to investigate how genetic and biological factors contribute to breast cancer risk among black women launched today. This collaborative research project will identify genetic factors that may underlie breast cancer disparities. The effort is funded by the National Cancer Institute (NCI), part of the National Institutes of Health.

The Breast Cancer Genetic Study in African-Ancestry Populations initiative does not involve new patient enrollment but builds on years of research cooperation among investigators who are part of the African-American Breast Cancer Consortium, the African-American Breast Cancer Epidemiology and Risk (AMBER) Consortium, and the NCI Cohort Consortium. These investigators, who come from many different institutions, will share biospecimens, data, and resources from 18 previous studies, resulting in a study population of 20,000 black women with breast cancer.

“This effort is about making sure that all Americans – no matter their background – reap the same benefits from the promising advances of precision medicine. The exciting new approaches to cancer prevention, diagnosis, and treatment ring hollow unless we can effectively narrow the gap of cancer disparities, and this new research initiative will help us do that,” said Douglas R. Lowy, M.D., acting director of NCI. “I’m hopeful about where this new research can take us, not only in addressing the unique breast cancer profiles of African-Ameri-

can women, but also in learning more about the origin of cancer disparities.”

Survival rates for women with breast cancer have been steadily improving over the past several decades. However, these improvements have not been shared equally; black women are more likely to die of their disease. Perhaps of most concern is that black women are more likely than white women to be diagnosed with aggressive subtypes of breast cancer. The rate of triple-negative breast cancer, an aggressive subtype, is twice as high in black women as compared to white women.

The exact reasons for these persistent disparities are unclear, although studies suggest that they are the result of a complex interplay of genetic, environmental, and societal factors, including access to health care. Large studies are needed to comprehensively examine these factors, and NCI is supporting several such efforts.

As part of the study, the genomes of 20,000 black women with breast cancer will be compared with those of 20,000 black women who do not have breast cancer. The genomes will also be compared to those of white women who have breast cancer. The project will investigate inherited genetic variations that are associated with breast cancer risk in black women compared to white women. In addition, researchers will examine gene expression in breast cancer tumor samples to investigate the genetic pathways that are involved in tumor development.

“This \$12 million grant—in combination

with previous investments—should help advance our understanding of the social and biological causes that lead to disparities in cancer among underserved populations,” said Robert Croyle, Ph.D., director of NCI’s Division of Cancer Control and Population Sciences (DCCPS), which is administering the grant. “A better understanding of the genetic contributions to differences in breast cancer diagnoses and outcomes among African-Americans may lead to better treatments and better approaches to cancer prevention.”

“A number of studies have suggested that genetic factors may influence breast cancer disparities, so we’re hopeful that this project can help to shed further light on this matter,” said Damali Martin, Ph.D., program director for the DCCPS Genomic Epidemiology Branch. Dr. Martin’s office is working directly with the grant recipients as well as the consortia groups that have been researching black women and breast cancer.

The grant has been awarded to Wei Zheng, M.D., Ph.D., of Vanderbilt University, Nashville, Tennessee; Christopher Haiman, Sc.D., of the University of Southern California, Los Angeles; and Julie Palmer, Sc.D., of Boston University. Additionally, minority scientists from various institutions, including from one Historically Black College and University medical school, are playing an important role in this study, and they have been involved in previous research that this study builds upon. For example, the Southern Community Cohort Study,

a contributing study for this grant, represents a 15-year partnership between Vanderbilt and historically black Meharry Medical College in Nashville, Tennessee. In addition, this grant will provide training opportunities for scientists from minority populations.

Support for ongoing research in this area represents NCI’s continued commitment to fund a comprehensive portfolio of research aimed at reducing cancer risk, incidence, and mortality, as well as improving quality of life for cancer survivors across all demographic groups.

The National Cancer Institute leads the National Cancer Program and the NIH’s efforts to dramatically reduce the prevalence of cancer and improve the lives of cancer patients and their families, through research into prevention and cancer biology, the development of new interventions, and the training and mentoring of new researchers. For more information about cancer, please visit the NCI website at www.cancer.gov or call NCI’s Cancer Information Service at 1-800-4-CANCER.

About the National Institutes of Health (NIH): NIH, the nation’s medical research agency, includes 27 Institutes and Centers and is a component of the U.S. Department of Health and Human Services. NIH is the primary federal agency conducting and supporting basic, clinical, and translational medical research, and is investigating the causes, treatments, and cures for both common and rare diseases. For more information about NIH and its programs, visit www.nih.gov.

Study Shows Association Between Breastfeeding and Reduced Risk of Breast Cancer

A large international study shows that breastfeeding is associated with a lower risk of developing an aggressive form of breast cancer called hormone-receptor negative. This new combined evidence shows the risk was reduced by up to 20% in women who breastfed. Published in *Annals of Oncology*, this breastfeeding meta-analysis is a collaboration between Breastcancer.org; Icahn School of Medicine at Mount Sinai; Washington University, St. Louis; and the American Cancer Society.

Hormone-receptor-negative (HRN) breast cancers are more likely to be aggressive and life-threatening. This subtype is more commonly diagnosed in women under age 50. Women of African American or Sub-Saharan African descent are more likely to be diagnosed with HRN breast cancers, as are women with the BRCA1 gene mutation. Other factors may put these women at even higher risk for developing HRN breast cancer, including obesity and multiple early pregnancies. Furthermore, women with these multiple risk factors are least likely to breastfeed.

In the United States, HRN breast cancers represent about 20% of all breast cancers. This subtype of breast cancer has no receptors for the hormones estrogen or progesterone; about two-thirds of these HRN cancers also have no receptors for HER2 (human epidermal growth factor receptor 2). Breast cancers with no receptors for estrogen, progesterone, or HER2 are called triple negative (TN).

HRN and TN breast cancer are more often

deadly because they tend to be diagnosed at later stages, respond to fewer treatment options, and are less likely to be cured by current therapies. In the absence of the receptors for estrogen, progesterone, and HER2, medicines that target these receptors—such as tamoxifen, aromatase inhibitors, Herceptin, and Perjeta—are ineffective and thus have no role in treating these patients.

“Further evidence to support the long-term protection of breastfeeding against the most aggressive subtypes of breast cancer is very encouraging and actionable,” said Marisa Weiss, M.D., president and founder, Breastcancer.org, and director of breast health outreach, Lankester Medical Center. “Breastfeeding is a relative-

ly accessible, low-cost, short-term strategy that yields long-lasting natural protection.”

This work highlights the need for more public health strategies that directly inform women and girls about the maternal (and fetal) benefits of breastfeeding before and during a woman’s child-bearing years. It’s also important for these women to have the message reinforced by their healthcare professionals.

It’s critical to remove the barriers to breastfeeding at home, in the community and in the workplace. “All approaches will be necessary in order to protect the most women against the devastation of breast cancer over their lifetimes,” said Farhad Islami, M.D., Ph.D., director of interventions, Surveillance and Health Ser-

vices Research, American Cancer Society.

“Pregnant women and young mothers are highly receptive and motivated to make healthy choices. We need to encourage women who are able to breastfeed to do so for their breast health, in addition to the health of their children,” said Paolo Boffetta, M.D., associate director for population sciences at the Tisch Cancer Institute at the Icahn School of Medicine at Mount Sinai. “Further prospective research will be necessary to further understand the full impact of breastfeeding duration and its effect on other subtypes.”

Information for this article was provided by Breastcancer.org.

TASK FORCE CONFIRMS THE VALUE OF SCREENING MAMMOGRAPHY

An updated US Preventive Services Task Force (USPSTF) recommendation has once again confirmed the value of screening mammography, concluding that the benefit of mammography outweighs the harms of screening in all age groups from age 40 through ages 74. It emphasizes that women and clinicians providing primary care to women both need to understand the benefits and harms of screening.

Compared to the initial draft recommendation, the USPSTF now places greater emphasis on the importance of making a personal, informed decision about when to start screening. The new language adds greater clarity regarding the higher risk of developing breast cancer in the late 40’s compared to the early 40’s and endorses a woman starting

to screen any time in that decade if she believes screening is right for her.

The ACS guideline and the USPSTF recommendation state similar recommendations, but there are a few areas of important differences, including the age by which all women should have started screening, the frequency of screening mammography, and at what age screening should stop.

While differences exist between recommendations from the USPSTF, the ACS and other organizations, each confirms the importance and value of regular screening mammography. Our nation has a vital opportunity to further reduce mortality from breast cancer by reducing barriers to screening for all women, and in particular to improve access to high quality

mammography to the more than one-third of women who are not being regularly screened.

The Affordable Care Act tied health insurance coverage policies to USPSTF guidelines. However, recent action in Congress placed a two-year moratorium on this breast cancer screening guideline. While insurance coverage for women who choose to have mammography in their 40s should not be interrupted in the next two years, concern remains about the implications of this updated guideline on insurance coverage decisions in the future.

Information for this article was provided by the American Cancer Society.

BREAST CANCER AWARENESS

Cancer Survivors: A Growing Population

There were more than 15.5 million Americans with a history of cancer as of January 1, 2016, a number that is projected to reach more than 20 million by 2026. That's according to Cancer Treatment and Survivorship Statistics, 2016, published in *CA: A Cancer Journal for Clinicians*, a peer-reviewed journal of the American Cancer Society, and its companion publication for consumers, *Cancer Treatment & Survivorship Facts & Figures, 2016-2017*. The report was released ahead of National Cancer Survivors Day, Sunday June 5, 2016.

Although overall cancer incidence rates are declining in men and stable in women, the number of cancer survivors continues to increase in the United States because of a growing and aging population, as well as increases in cancer survival because of advances in early detection and treatment.

The report is produced every two years in collaboration with the National Cancer Institute to estimate the numbers of current and future cancer survivors to help the public health community better serve this unique population, many of whom cope with long-term physical effects of treatment as well as psychological and socioeconomic sequelae.

The three most prevalent cancers in 2016 are prostate (3,306,760), colorectal (724,690), and melanoma (614,460) among men and breast (3,560,570), uterine corpus (757,190), and colorectal (727,350) among women. The distribution of prevalent cancers (the number of previously diagnosed cancers among people who are alive) differs from incident cancers (the number of newly diagnosed cancers).



For example, lung cancer is the second most commonly diagnosed cancer in men, but ranks eighth in prevalence, largely because of poor survival.

One-third of survivors in the U.S. today were diagnosed less than five years ago and more than one-half (56%) were diagnosed within the past 10 years. Nearly half (47%) are

age 70 years or older, although age distribution varies by cancer type. For example, the majority of prostate cancer survivors (64%) are age 70 years or older, compared to just one in three (37%) melanoma survivors. The report estimates that there are 65,190 cancer survivors aged 14 and under and 47,180 aged 15 to 19 years in the United States.

In the article, the term "cancer survivor" is used to describe a person who has a history of cancer, from the time of diagnosis through the remainder of his or her life. It includes patients currently undergoing treatment and those who may have become cancer-free. It is important to note that not all people with a history of cancer identify with the term "cancer survivor."

"People with a history of cancer have unique medical and psychosocial needs that require proactive assessment and management by primary care providers," write the authors. "Although there are a growing number of tools that can assist patients, caregivers, and clinicians in navigating the various phases of cancer survivorship, further evidence-based resources are needed to optimize care."

The report says identification of the best practices for delivering quality posttreatment cancer care is needed and points to ongoing efforts by the American College of Surgeons, the Alliance for Quality Psychosocial Cancer Care, and the American Cancer Society (ACS). The ACS has begun to produce guidelines to assist primary care and other clinicians in the provision of care for people with a history of cancer.

For more information, visit cancer.org.

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BREAST CANCER AWARENESS

Uncovering a New Principle in Chemotherapy Resistance in Breast Cancer

A laboratory study has revealed an entirely unexpected process for acquiring drug resistance that bypasses the need to re-establish DNA damage repair in breast cancers that have mutant *BRCA1* or *BRCA2* genes. The findings, reported by Andre Nussenzweig, Ph.D., and Shyam Sharan, Ph.D., at the National Cancer Institute (NCI), part of the National Institutes of Health, and colleagues, appeared July 21, 2016, in *Nature*.

In normal cells, the proteins *BRCA1* and *BRCA2* act as DNA damage sensors, surveyors, and responders. They help perform complex functions that facilitate the repair of damaged DNA. Individuals who inherit certain mutations in either the *BRCA1* or *BRCA2* gene have defective DNA repair and an increased risk of developing breast, ovarian, and other cancers. Specifically, mutations in *BRCA1* and *BRCA2* account for 20 percent to 25 percent of hereditary breast cancers and 5 percent to 10 percent of all breast cancers. The reduced ability to repair breaks in DNA in cells with a *BRCA1* or *BRCA2* mutation makes the cells sensitive to DNA damaging drugs. However, breast cancers eventually acquire resistance to these drugs. One documented mechanism for developing chemoresistance in such tumors is through the restoration of accurate DNA repair pathways that mend DNA breaks caused by chemotherapy.

Nussenzweig's laboratory has spent the past decade trying to understand the cellular mechanisms that regulate DNA repair in normal and pathogenic states. "It is the intricate mechanisms that tumor cells evolve to bypass the need for accurate DNA repair that form the foundation of our study," said Nussenzweig. "A deeper knowledge of the processes that drive drug resistance in *BRCA1/2*-mutant tumors will

lead to novel therapeutic approaches that target tumor-specific vulnerabilities."

In this study, the researchers linked the protection and stabilization of DNA replication forks as a major contributory mechanism to drug resistance in *BRCA1/2*-mutant breast and ovarian cancers. Replication is a cellular process that produces two indistinguishable DNA copies from a single DNA molecule. This DNA-copying process is an essential step in cellular division and occurs at defined locations called replication forks.

The movement of a replication fork as it migrates along a DNA molecule can be disrupted by the presence of a diverse group of DNA structures and proteins, collectively and loosely referred to as replication fork barriers. This interruption of replication fork migration results in what is called a stalled fork. Upon replication fork stalling, the *BRCA1* and *BRCA2* proteins are called upon to protect the newly synthesized strands of DNA. If these proteins are absent, the replication fork is destabilized and the newly synthesized DNA is degraded, which increases genomic instability and increases sensitivity to DNA-damaging drugs.

The investigators were able to identify other proteins, such as PTIP, CHD4 and PARP1, that actively promote replication fork destabilization through the recruitment of enzymes that degrade newly synthesized DNA. The absence of these proteins protected the DNA at replication forks and remarkably reversed the drug sensitivity of both *BRCA1*- and *BRCA2*-mutant cells, making them chemoresistant. These studies also highlighted the complex ways by which tumor cells can evade chemotherapeutic interventions and acquire drug resistance, since disrupting the activity of multiple proteins led to the same end point of replication fork protection. These



results are of particular relevance in the clinical setting, where expression of these proteins appears to be an indicator of how patients with *BRCA1*- and *BRCA2*-mutant cancers will respond to chemotherapeutic treatment with DNA-damaging agents.

All together, these results underscore the importance of replication fork barriers to genomic instability and drug sensitivity in the context of *BRCA1/2* mutations. The results also suggest that the cellular levels of these proteins could be used as a prognostic factor in acquired resistance in *BRCA1/2*-mutant cancers.

"Our work is starting to not only refine, but also redefine, the current dogma in

the field, which states that restoring DNA repair pathways are the only means by which *BRCA1/2*-mutant cells can become chemoresistant," concluded Nussenzweig.

Information for this article was provided by the National Cancer Institute, which leads the National Cancer Program and the NIH's efforts to dramatically reduce the prevalence of cancer and improve the lives of cancer patients and their families, through research into prevention and cancer biology, the development of new interventions, and the training and mentoring of new researchers. For more information about cancer, please visit the NCI website at www.cancer.gov.

New American Cancer Society Breast Cancer Book Offers Hope for the Recently Diagnosed

The American Cancer Society last month announced the publication of *Breast Cancer Clear & Simple, Second Edition: All Your Questions Answered*, an engaging, question-and-answer book written to help newly diagnosed patients quickly digest the crucial information needed to navigate through their breast cancer experience.

Breast Cancer Clear & Simple was written to help women with breast cancer and their care-

givers know what to expect, what to do, and how to get through what can be an overwhelming, life-changing experience. Professional illustrations throughout the book can help patients understand how breast cancer starts in the body, facts about breast anatomy, the lymph system, and the types of breast reconstruction available.

"When women are diagnosed with breast cancer, they have a lot to think about and a

seemingly endless amount of decisions to make. This book supports them by providing a comprehensive and easy-to-understand format to help them navigate through their diagnosis and treatment options, especially during those first days and months," said Dr. Richard Wender, chief cancer control officer, American Cancer Society.

Written by medical experts from the American Cancer Society, with guidance from breast

cancer survivors, this evidence-based book is a great resource for any breast cancer patient.

"This book is an important and innovative tool to support patients with a breast cancer diagnosis to help them make the treatment choices that are right for them," said Dr. J. Leonard Lichtenfeld, deputy chief medical officer, American Cancer Society.

Breast cancer remains the most frequently diagnosed cancer in women. This year, invasive breast cancer will be diagnosed in about 246,660 women. An additional 61,000 new cases of in situ breast cancer will be diagnosed. Survival rates are generally higher for women with earlier-stage cancers.

Breast Cancer Clear & Simple, Second Edition: All Your Questions Answered is available in both print and eBook formats.

Breast Cancer Clear & Simple, Second Edition: All Your Questions Answered By: *The American Cancer Society* Published: August 22, 2016 ISBN-13: 978-1604432367 Pages: 208 Price: \$14.95 USD and \$17.95 CAN (hardcopy)

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BREAST CANCER BY THE NUMBERS

- About 1 in 8 U.S. women — 12.4% — will develop invasive breast cancer over the course of her lifetime.
- In 2016, an estimated 246,660 new cases of invasive breast cancer are expected to be diagnosed, along with 61,000 new cases of non-invasive breast cancer (also known as carcinoma in situ). About 40,450 women are expected to die in 2016 from breast cancer, though there has been a decrease in death rates since 1989, with larger decreases in women under 50. These decreases are thought to be the result of treatment advancements, earlier detection through screening, and increased awareness.
- For women in the United States, breast cancer death rates are higher than death rates for any other type of cancer, besides lung cancer.
- Except for skin cancer, breast cancer is the most

commonly diagnosed cancer among American women. Just under 30% of cancers diagnosed in women are breast cancers.

- In women under 45, breast cancer is more common in African-American women than white women. Overall, African-American women are more likely to die of breast cancer. Asian, Hispanic, and Native-American women have a lower risk of developing and dying from breast cancer.
- As of early 2016, there were more than 2.8 million women with a history of breast cancer in the U.S. This figure includes women currently being treated and women who have finished treatment.
- A woman's risk of breast cancer approximately doubles if she has a first-degree relative (mother, sister, daughter) who has been diagnosed with breast cancer.

- Less than 15% of women who get breast cancer have a family member who has been diagnosed with it.
- About 5-10% of breast cancers are thought to be caused by inherited gene mutations (abnormal changes passed through families).
- Mutations of the *BRCA1* and *BRCA2* genes are the most common. Women with a *BRCA1* mutation have a 55-65% risk of developing breast cancer before age 70, often at a younger age than it typically develops. For women with a *BRCA2* mutation, the risk is 45%. An increased ovarian cancer risk is also associated with these genetic mutations.
- The most significant risk factors for breast cancer are gender (being a woman) and age (growing older).

Information provided by the American Cancer Society.